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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,807	12/05/2000	Michael Wayne Graham	0763/74768-B-PCT-US/JPW/G	1584

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/646,807	GRAHAM ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/28/06,1/28/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,57,59,60,62,63 and 65-107* is/are pending in the application.

4a) Of the above claim(s) *57,59,63,68-74 and 102-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,60,62,65-67,75-101 and 107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/27/08,1/28/08,12/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the papers filed 12/17/07, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Ming-Bo Wang and Peter Michael Waterhouse.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Third-party submission filed under 37 CFR 1.99

A third-party submission has been filed under 37 CFR 1.99 on 2/28/08 in the published application.

To ensure that a third-party submission does not amount to a protest or pre-grant opposition, 37 CFR 1.99 does not permit the third party to have the right to insist that the examiner consider any of the patents or publications submitted. Furthermore, if the submission or part of the submission is not in compliance with 37 CFR 1.99, that noncompliant submission or part thereof will not be entered in the application file. Therefore, unless the examiner clearly cites a patent or publication on form PTO-892, Notice of References Cited and such reference is used in a rejection or its relevance is actually discussed during prosecution, consideration by the examiner of any patent or publication submitted in a third-party submission cannot be presumed.

If the applicant wants to ensure that the information in a third-party submission is considered by the examiner, the applicant should submit the information in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98. An individual who has a duty to disclose under 37 CFR 1.56 should also submit any material information contained in a third-party submission to the Office in an IDS in compliance with 37 CFR 1.97 and 37 CFR 1.98 to ensure such material information is properly disclosed to the examiner.

Election/Restrictions

Newly submitted or amended claims 57, 59, 63, 68-74, and 102-106 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the response to the election/restriction mailed on 12/24/02 is directed to the elected invention comprising a target gene in an animal cell, wherein the target gene is endogenous to the animal cell.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57, 59, 63, 68-74, and 102-106 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/28/06 was filed after the mailing date of the non-final rejection on 6/28/06. The submission is in compliance

with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The exhibits as civil ligation actions have been considered, but the documents cited in the exhibits have not been considered for the reasons set forth in the previous office action. See office action mailed on 6/28/06.

The Wagner reference in the information disclosure statement filed 1/28/08 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the date of the Wagner reference is missing. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

The references cited in the Partial European Search Report dated 11/2/07 have been considered, and will be listed on any patent resulting from this application because they were provided on a separate list in compliance with 37 CFR 1.98(a)(1).

The references cited in the European Search Report 6/3/05; Hungarian Search Report dated 7/13/04, International Search Reports dated 3/16/01 and 9/27/02 have been considered, but will not be listed on any patent resulting from this application

because they it appears that the references were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO/SB/08A and 08B form, must be filed within the set period for reply to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81, 82, and 83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New Matter:

There does not seem to be support for the limitation 'the stuffer comprises an intron' in claim 81. See MPEP § 2163.06. Applicant cites several pages in the specification for support for of the new claim, but does not specifically indicate where the limitation in claim 81 has support. The examiner had to search the entire specification for the limitations. It appears that the only support for the limitations is on pages 15-16. However, on page 15, line 30 to page 16, line 8 specifically recites: wherein the nucleic acid sequence comprises intron/exon splice junction sequences the

stuffer fragment may serve as an intron sequence placed between the 3'-splice site of the structural gene nearer the 5'-end of the gene and the 5'- splice site of the next downstream unit thereof. Thus, it appears that the specification only provides support for using an intron as the stuffer between a sequence comprising intron/exon splice junction sequence. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

There does not seem to be support for the limitation 'no more than 2.0 kilobases' in claim 82 and the limitation 'no more than 0.5 kilobases (kb)' in claim 83. See MPEP § 2163.06. Applicant cites several pages in the specification for support for all the amended and new claims, but does not specifically indicate where the limitation in claims 82 and 83 have support. The examiner had to search the entire specification for the limitations. It appears that the only support for the limitations is on page 29, lines 19-21. However, on page 29, lines 19-21 the support is for no more than 0.5-2.0 kb, not no more than either 0.5kb or 2.0kb with no lower limit. Thus, it appears that the specification only provides support for no more than 0.5-2.0 kb not below 0.5kb. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 56, 60, 62, 65-67, 75-101, and 107are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 88 recites the limitation "the 3' end" in line 2. There is insufficient antecedent basis for this limitation in the claim.

The term "in a head to head orientation relative to each other" or "a tail to tail orientation relative to each other" in claims 84and 85, respectively, is a relative term which renders the claim indefinite. The term "in a head to head orientation relative to each other" or "a tail to tail orientation relative to each other" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term are indefinite since it is not defined what part of the sequence is considered the head or tail.

Claims 56, 60, 62, 65-67, 75-101, and 107 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: genetic construct comprising two copies of a structural gene sequence having greater than 20 consecutive nucleotides which is identical in sequence to greater than 20 consecutive nucleotides of said target gene, wherein one copy is placed in the antisense orientation. It is not apparent how two copies of a structural gene can be identical when one copy is in the antisense orientation form.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The claimed invention is directed to a mammalian cells comprising a genetic construct comprising a first nucleotide sequence having 20 consecutive nucleotides identical to a region of a target gene; a second nucleotide sequence having 20 consecutive nucleotides complementing the first nucleotide sequence, a stuffer fragment that linked that first and second nucleotide sequence, and a transcription terminator; a promoter operably linked to the first and second nucleotide sequences and stuffer fragment.

With respect to the term “stuffer fragment”, the instant specification defines the term (see pages 15-16) and the term could read on a single segment of a nucleic acid separating two other nucleotide sequences.

Claims 56, 60, 62, 65-67, 75-80, 82, 84-101, and 107 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al (US 6,506,559, cited on a PTO-1449). Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising dsRNA comprising a sense strand and an antisense strand of the target gene (columns 4 and 9). The structural gene can comprise one or

more strands of the nucleotide sequence (column 4). The dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7). A single self-complementary strand would indicate that the two nucleotides are sequences which would read on a stuffer between the two sequences. In addition, Fire taught self-complementary RNA strands of greater than 400 bases, e.g., 25 consecutive nucleotides were identical to a sequence of a region of a target mRNA sequence, and another 25 consecutive nucleotides were complementary to that target sequence. In such a molecule, an arbitrary number of nucleotides associated with the inherent hairpin region of the RNA strand can be arbitrarily considered to be a stuffer fragment that links 25 complementary base pair. This molecule could have stuffer regions of 10, 50, 100 nucleotide bases on the arbitrary designation of what is, and what is not, the stuffer sequence. The construct comprises a regulatory region including polyadenylation (columns 8-9). The nucleotide sequence may be at least 25 or 50 bases (column 8). The vector can be introduced into a cancerous cell, including cancer cells find in humans (column 9-10). A viral vector or lipid mediated carrier transport can be used as the vector (column 9). The target gene can be a transgene, a vertebrate, invertebrate, fish, mammal, human, or insect gene (columns 4, 8, and 10). The structural gene can be less than 2.0 kilobases (Table 1 and Figure 1).

The 102(e) reference is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention. An affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable invention, see MPEP § 2306. If the reference and this application are

not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718.

Applicant's arguments filed 12/28/06 have been fully considered but they are not persuasive

In response to applicant's argument that Fire neither teaches nor contemplates the use of a stuffer fragment to spatially separate the two structure genes, the argument is not found persuasive because Fire teaches that the dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7). The dsRNA formed by a single self-complementary RNA strand would require a loop to connect the two RNA strands. The loop would read on the stuffer sequence separating the two structural sequences.

In response to applicant's argument that Fire does not teach length limitation of 20 consecutive nucleotides identical in sequence to 20 consecutive nucleotide of a target gene or the stuffer fragment, which separates the two copies, the argument is not found persuasive because the length limitation in the instant claims is not limited 20 consecutive nucleotides. The length limitation is directed to greater than 20 consecutive nucleotides, which reads on the dsRNA taught by Fire.

In response to applicant's argument that Fire does not teach reducing the expression of a target gene in a plant cell using the claimed dsRNA, the argument is not

found persuasive because the claims directed to a plant are considered withdrawn to a non-elected invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 56, 62, and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al (US 6,506,559, cited on a PTO-1449) taken with German et al. (US 6,225,290). Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising a sense strand and an antisense strand of the target gene (columns 4 and 9). The construct comprises a regulatory region including polyadenylation (columns 8-9). The nucleotide sequence may be at least 25 or 50 bases (column 8). The vector can be introduced into a cancerous cell, including cancer cells find in humans (column 9-10). The target gene can be an endogenous from in a human cell (columns 4 and 10-11). The structural gene can comprise one or more strands of the nucleotide sequence (column 4). However, Fire does not specifically teach separating a construct comprising the structural gene sequences with a stuffer sequence comprising an intron, wherein the stuffer sequence spatially separates the gene sequences. In view of the breadth of the term “two copies are spatially separated by a s stuffer fragment which comprises an intron” the term reads on the stuffer being located between the two sequences including the stuffer being located before the first structural gene in a circular plasmid.

However, at the time the invention was made, German teaches that including one or more introns in a construct can increase the level of expression of a DNA of interest in the construct (columns 7-8). German teaches inserting the intron into the construct at a 5' position to the DNA of interest (Column 8).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with German,

namely to produce an isolated animal cell comprising a construct comprising a structural gene with a stuffer sequence comprising an intron. One of ordinary skill in the art would have been motivated to combine the teaching to improve the efficient of expression of the structural genes by placing an intron 5' to each structural gene.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 56, 60, 62, 65, 66, 67, 75-78, 80, 84-90, 96, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, cited on an IDS) in view of Kool (US 5,514,546, cited on an IDS).

In view of the 112 second paragraph rejection on the independent claim, Agrawal could read on the claimed product because the claimed product could read on a RNA hairpin comprising a region that is complementary to a target region of a gene in a cell and a region that is self-complementary.

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The size of the self complementary region may vary, but may be so extensive as to involve every nucleotide of the oligonucleotide, i.e. it may be 8-50 nucleotides in length (see page 15, lines 3-6, 16-21, and 26-30). The resulting RNA may form a hairpin structure comprising a loop,

see page 15, lines 12-16, and Fig. 1. The loop is considered to be a "stuffer" sequence. Thus, Agrawal fairly taught a double stranded RNA comprising a target hybridizing region of 8-50 ribonucleotides, a loop, and a self-complementary region of 8-50 nucleotides. The target gene may be a cellular gene or gene transcript, see page 12. Absent evidence of unexpected results, it would have been obvious to one of ordinary skill in the art to vary the length of the unpaired loop sequence of the self-stabilizing RNA of Agrawal in order to optimize hybridization of the complementary section of the oligonucleotides, thereby providing increased stability against nucleolytic attack. However, Agrawal does not explicitly teach vectors encoding the antisense oligonucleotides, oligonucleotides targeting a coding region, or liposome-containing compositions.

However, at the time the invention was made, Kool taught delivery of stem-loop oligonucleotides by expression vector or by direct application of the oligonucleotides. See abstract; Fig. 1; column 3, lines 16-19 and lines 58-62; column 4, lines 6-17; and column 14, lines 39-. Kool also disclosed antisense inhibition by targeting coding regions. See column 7, lines 43-46. Kool also disclosed delivery of expression vectors by viral- or liposome-mediated transfection. See column 15, lines 36-45; column 16, lines 43-47; paragraph bridging columns 24 and 25; and column 29, lines 32 and 33.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the oligonucleotides of Agrawal by use of the expression vector of Kool. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such

elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Thus the delivery techniques of Kool, i.e. direct application of oligonucleotides, and transfection of oligonucleotide expression vectors, are considered to be exchangeable equivalents. Alternatively, the method of delivering the oligonucleotides can be viewed as a matter of design choice. Moreover, one would have been motivated to use the expression vector of Kool in order to obtain continuous synthesis and action of oligonucleotides for the amount of time that the vector was present in the cell. Generally, expression vectors can be made with selectable markers that allow their maintenance in a cell for a longer time than the expected lifetime of an oligonucleotide. Thus, one of ordinary skill in the art could reasonably expect to obtain antisense inhibition for a longer period of time with the expression vector of Kool.

It would have been similarly obvious to target coding regions of target genes, and to deliver the vectors by viral or liposomal means as suggested by Kool. See KSR v. Teleflex, Id.,

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 56, 62, 79, 89, 91, and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of McGarry et al (Proc Nat. Acad. Sci. USA 83:399-403, 1986).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not teach RNA molecules comprising an intron, or RNA molecules directed against an RNA in a cell of an invertebrate animal or insect.

McGarry taught methods of inhibiting gene expression by expression of antisense RNA in cultured Drosophila cells.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of McGarry by designing an expression construct encoding a self-stabilizing RNA molecule as taught by Agrawal. One would have been motivated to do so in order to increase the stability of the antisense RNA, thereby providing a reasonable expectation of improving antisense performance.

Buchman taught that the inclusion of an intron in an expression construct could stimulate transcription of the expressed by 400-fold. See abstract,.

It would have been obvious to include an intron in the expression vector of McGarry in order to obtain the benefit of increased expression as taught by Buchman. The resulting transcripts would contain, prior to processing, an intron.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 56, 62, 89, 92, and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of Barabino et al (Mech. Dev. 63: 133-143, 1997).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not teach RNA molecules directed against an RNA in a cell of an aquatic animal.

Barabino taught methods of suppressing Alx gene expression in zebrafish embryos by administration of antisense oligonucleotides. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Barabino by designing and using expression vectors encoding self-stabilizing antisense RNA molecules as taught by Agrawal. One would have been motivated to do so in order to increase antisense performance.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 56, 62, 89, and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al (WO 94/01550, of record) in view of Swamynathan et al (J. Virol. 71(4): 2873-2880, 1997).

Agrawal taught self-stabilizing RNA molecules comprising a region that is complementary to a target in a eukaryotic mRNA in a human cell and a region that is self-complementary. See abstract; page 8, lines 7-11 and 22-24, paragraph bridging pages 11 and 12, and page 13, lines 25-30. The target hybridizing region is from 8 to 50 nucleotides in length (sentence bridging pages 9 and 10). The self complementary regions may be separated by an unpaired loop structure (see e.g. Fig. 1, and page 15, lines 9-16).

Agrawal did not teach RNA molecules directed against an RNA in a cell of an avian animal.

Swamynathan taught a method of inhibiting expression of chicken YB-2 in avian fibroblasts by administration of antisense RNA directed against the ama-1 gene. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Swamynathan by designing and using self-stabilizing antisense RNA molecules as taught by Agrawal. One would have been motivated to do so in order to increase antisense performance.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 56, 60, 62, 65-67, 75-101, and 107 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5, 6, and 11-22 of U.S. Patent No. 6,573,099. Although the conflicting claims are not identical, they are not patentably distinct from each other because for reasons set forth in paragraph bridging pages 14-15 of the office action mailed on 3/7/03.

Applicant's arguments filed 11/30/06 have been fully considered but they are not persuasive because applicant did not address the rejection.

Claims 56, 60, 62, 65-67, 75-101, and 107 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-36, 38, 40, 53-55, 57, 59, 66, 74-76, 80-83, 92-94, 96, 98-99 of copending Application No. 10/346,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims embrace an isolated genetic construct comprising at least two copies of a structural gene sequence, wherein the structural gene sequence comprise a nucleotide sequence which is identical to at least a region of said target gene, wherein at least two copies of the structural gene sequence are placed under the control of a promoter, wherein one or more copies is placed operably in the sense orientation under the control of at least one promoter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 56, 60, 62, 65-67, 75-101, and 107 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48, 107, 110, 111, 114-136, 138, and 146-149 of copending Application No. 10/646,070. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are directed to a gene construct comprising a single promoter operably linked to at least two structural genes comprising greater than 20 consecutive nucleotides that are identical to a nucleotide sequence from

an animal cell, wherein one structural gene is in the sense orientation to the promoter and another structural gene is placed in an antisense orientation to the promoter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 56, 60, 62, 65-67, 75-101, and 107 are directed to an invention not patentably distinct from claims 34-36, 38, 40, 53-55, 57, 59, 66, 74-76, 80-83, 92-94, 96, 98-99 of commonly assigned US application 10/346,853. Specifically, for the reasons set forth under the provisional obviousness double patenting rejection.

Claims 56, 60, 62, 65-67, 75-101, and 107 are directed to an invention not patentably distinct from claims 48, 107, 110, 111, 114-136, 138, and 146-149 of commonly assigned US application 10/646,070. Specifically, for the reasons set forth under the provisional obviousness double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US applications, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were

commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635